

## Remarks

Claims 1-6, 9-13 and 23-38 were pending in the above-mentioned application. Claims 4, 5, 12, 13, 23, 27-30 and 38 have been cancelled without prejudice.

Claim 1 has been amended to combine the wording of previous claims 1 and 4 and the specification page 24, lines 13-24, page 25, lines 19-21, page 26, lines 7-10 and lines 28-32. This limits the contrast generating species to magnetic resonance contrast generating species (basis in the specification page 15, last paragraph where magnetic resonance is mentioned as a particularly preferred embodiment) and disclaims gas or gaseous precursors in order to further discriminate Applicants invention from the prior art.

Claim 2 has been amended to include the term "oxygen tension". Page 16, 2<sup>nd</sup> paragraph of the specification serves as a basis for this amendment.

Claim 6 has been amended to incorporate the list of MR contrast generating species described on page 28, line 26-30 of the specification.

Claim 10 has been amended to include the term "liposome" as described on page 22, line 4; page 32, 3<sup>rd</sup> paragraph and in the Examples 1-6, 8-22, 26-27 and 29 of the specification.

Claim 11 has been amended to include the membrane materials described on page 24, line 11-13 of the specification.

Minor amendments were made to the wording of claim 24 in order to more distinctly claim the present invention.

Claim 26 has been amended to include the compounds described on page 35, line 3-4 of the specification.

Minor amendments were made to the wording of claim 31 and 32 in order to more distinctly claim the present invention.

Claim 37 has been amended by combining the wording of previous claims 1 and 4 and the specification page 24, lines 13-24, page 25, lines 19-21, page 26, lines 7-10 and lines 28-32. and the specification page 25, lines 19-21 and page 24, lines 13-24. This limits the contrast generating species to magnetic resonance contrast generating species (basis in the specification page 15, last paragraph where magnetic resonance is mentioned as a particularly preferred embodiment) and disclaims gas or gaseous precursors in order to further distinguish Applicants' invention from the prior art.

New claims 39-68 have been added. Basis for new claims 39-45 can be found in the specification on page 28, line 30-37, page 29, line 1-3 and page 29, last paragraph. Basis for new claim 46 can be found in the specification page 16, line 3.

Basis for new claim 47 can be found in the specification page 35, line 3-4 and in previous claim 26. Basis for new claim 48 can be found in the specification page 31, last paragraph and page 32. Basis for new claim 49 can be found in the specification page 39, line 18 and page 40. Basis for new claim 50 can be found in previous claim 2 and in the specification page 16, 2<sup>nd</sup> paragraph. Basis for new claim 51 is unchanged claim 3. Basis for new claims 52-60 are amended claim 6 and new claims 39-46. Basis for new claim 61 and 62 are amended claims 11 and 10. Basis for new claims 63-65 are new claims 47-49. Basis for new claim 66 is amended claim 26. Basis for new claim 67 is unchanged claim 9. Basis for new claim 68 are the membrane and matrix materials explicitly mentioned in the Examples 1, 2, 12,16, 22 and 30 and in the specification page 41, line 17 and the magnetic resonance contrast generating species explicitly mentioned in the Examples 1, 10, 13, 17 and in the specification page 29, line 23.

Upon entry of the above-made amendments and new claims, therefore, claims 1-1-3, 6, 10-11, 24-26, 31-37 and 39-68 will be pending in the current application. A clean copy of the claims encompassing the amendments and the newly added claims, is attached hereto.

The Office is hereby authorized to charge deposit account 502-590 for any fees incurred by entry of the new claims.

The amendments and the newly added claims are fully supported in the specification as originally filed and do not add new matter in contravention of 35 U.S.C. §132. Applicants respectively request that the amendments and new claims be entered.

The following remarks, in conjunction with the above amendments, are believed to be fully responsive to the outstanding Official Action.

**THE REJECTION UNDER 35 U.S.C § 103(a) SHOULD BE WITHDRAWN**

Claims 1-6, 9-13 and 23-28 are rejected under 35 U.S.C § 103(a) as being unpatentable over Unger I (6,315,981) in view of Ozer et al. (European J. of Pharm. And Biopharm.) or Sonek (5,631,141) in further view of Unger II (6,143,276). This rejection is respectfully traversed.

The present invention claims a method of imaging of an animate human or non-human animal body. The method includes the steps of parenterally administering to the body a particulate material comprising a matrix or membrane material and at least one magnetic resonance contrast generating species, generating MR image data of at least part of the body in which the species is present, and generating therefrom a signal indicative of the value or variation of the parameter in the part of the body.

The magnetic resonance contrast generating species of the present invention is neither a gas nor a gaseous precursor. The matrix or membrane material is responsive to a pre-selected physiological parameter and the response is an increased matrix or membrane permeability or chemical or physical breakdown of said matrix or membrane material, so as to alter the contrast efficacy of the species in response to a change in the value of the parameter.

Unger I, on the other hand, discloses microspheres filled with gas or a gaseous precursor which are used as MR contrast agents in MR imaging. As stated in column 4,

line 61-63, those microspheres are effective MR contrast agents. Unger I points out that the microspheres must be flexible for optimal results, i.e. that the gas or gaseous precursors must be encapsulated and stabilized by a flexible compound. Non flexible encapsulation compounds may break upon circulation in the body and the encapsulated gas will be lost, which in turn limits the effective period of time for which useful contrast can be obtained in vivo from the contrast agent (see column 4, lines 23-36). Unger I clearly states that microspheres comprising an encapsulation material which responds to a physiological parameter by showing an increased permeability or by a chemical or physical breakdown are not desirable as the encapsulated gas or the encapsulated gaseous precursor will be lost and contrast is no longer be obtained in vivo. This is supported by figures 5, which shows that upon loss of gas the contrast efficacy of the microspheres dramatically decreases. It is further supported by the statement that “ the microspheres are formed from a matrix of stabilizing compounds which permit the gas filled microspheres to be established and thereafter retain their size and shape for the period required to be useful in magnetic resonance imaging” (see column 7, lines 18-23). Thus, a matrix or membrane material which shows an increase in permeability or which chemically or physically breaks down in response to a change in a physiological parameter in a human or animal body is clearly not within the scope of Unger I. Moreover, no suggestion can be found in Unger I to use such matrix or membrane materials. In fact, Applicants respectfully submit that Unger I teaches away from using matrix materials as described in claim 1 of the present invention.

Hence, Applicants respectfully submit that Unger I neither contains a suggestion to use matrix material as stated in claim 1 of the present invention nor provides motivation to one of ordinary skill in the art to modify Unger I according to the teachings of Ozer. Ozer describes the release of drugs from drug loaded temperature- or pH-sensitive liposomes which is due to the dramatic increase of permeability of the liposome membrane at a temperature or pH where the matrix or membrane molecules of said liposome rearranges. The skilled person would immediately have recognized that modifying the matrix of the Unger I microspheres according to the disclosure of Ozer would have resulted in gas loaded microspheres which lose gas at a certain pH or temperature in the body. Such modified microspheres would no longer be effective MR contrast agents as Unger I teaches. Therefore, there is no motivation to modify the teaching of Unger I according to the teaching of Ozer.

In a similar manner, one of ordinary skill in the art would not have been motivated to modify Unger I according the teachings of Sonek. Sonek discloses spherical vesicles which comprise a membrane material that undergoes a phase transition at a certain temperature. Such vesicles are used to measure temperature in an in-situ microthermometry method. As the Examiner states these phase transitions involve substantial changes in the organization and motion of the compounds forming the membrane material. The skilled person would immediately have recognized that modifying the matrix of the Unger I microspheres according to the disclosure of Sonek would result in gas loaded microspheres which lose gas at a certain temperature in the

body and would thus be no longer effective MR contrast agents. Therefore, there is no motivation to modify the teaching of Unger I according to the teaching of Sonek.

Therefore, Applicants respectfully point out that even upon combining all prior art references, those combined teachings do not disclose, teach or suggest all the present claim limitations. As noted above, gases or gaseous precursors are disclaimed from the magnetic resonance contrast generating species in the independent claims 1 and 39 of the present invention. Unger I is directed to gaseous precursors and the Ozer and Sonek references fail to correct the cited deficiencies of the Unger I reference.

Finally, the Examiner pointed out that Unger II was relied upon for his teachings of targeting by attaching cell adhesion molecules to microspheres containing gaseous precursors. Applicants respectfully submit that that the current independent claims are not obvious over the cited prior art. As the independent claims 1 and 37 are believed to be patentable, subclaims directed to a combination of the particulate material claimed in claim 37 and the method claimed in claim 1 with a targeting ligand for a cell or a receptor of interest (subclaims 67 and 9) are likewise patentable.

Therefore, as none of the cited references, either singly or in combination, disclose, teach, or suggest the present invention, Applicants respectfully submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection is respectfully requested.

## Conclusion

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims, including claims 1-3, 6, 10, 11, 24-26, 31-37, and 39-68, are in condition for allowance. Favorable action thereon is respectfully requested.

The Office is hereby authorized to charge deposit account 502-590 for any fees incurred by the entry of this amendment, including but not limited to charges for the new claims.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,



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